

***Remarks***

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 1, 2, 4-10, 13, 16-18, 20, 21, 23, 25-27, 29-42, 44-56, 60, and 61 are pending in the application, with claim 1 being the independent claim. Claims 29-31, and 35-37 are withdrawn from prosecution. As process claims which depend from and include all the limitations of the product claims currently under examination, Applicants reserve the right to request rejoinder and examination of the withdrawn claims should the product claims be found allowable. Claims 28, 43, and 57-59 are sought to be cancelled without prejudice to or disclaimer of the subject matter therein. Applicants reserve the right to pursue the subject matter of all earlier pending claims in related applications. These changes are believed to introduce no new matter, and their entry is respectfully requested.

Claims 1, 5, 13, 17, 23, 27, 34, 44, 45, 50, 53, 54, 55, 56, and 61 have been amended. Support for the amendment to claim 1 adding the limitation "wherein said complex adopts a micro-particle structure in the form of a cage-like matrix" can be found in the specification at paragraph [0133], and also in International Patent Application No. PCT/DK02/002299, which corresponds to the U.S. Patent Application No. 10/114,957 (Publication No. US 2003/0118635 A1), allowed on December 4, 2009 (hereinafter "Dalsgaard") on page 22, lines 21-24, which is incorporated into the instant application by reference in paragraph [0126]. Additional amendments to claim 1, as well as amendments to claims 50, 53, 54, and 55 merely clarify the language of the claims, and are not believed to alter the scope or subject matter of the claims in any way. Amendments are sought to claims 13, 44, 45, and 61 to correct dependencies and to

maintain proper antecedent basis. Amendments are sought to claims 5, 17, and 27 to correct minor grammatical errors. Support for the amendment to claim 23 can be found in the original claim 23, as filed. Support for the amendment to claim 34 can be found in the original claim 32, as filed. Support for the amendment to claim 56 can be found in the specification at paragraph [0013]. Accordingly, no new matter has been added by these amendments.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

***Rejections Under 35 U.S.C. § 102(b)***

The Examiner rejected claims 1, 2, 4, 5, 9, 10, 13, 16-18, 20, 21, 23, 25-27, 32, 34, 38-43, 46, 47, 49-55, and 57-61 under 35 U.S.C. § 102(b) as allegedly being anticipated by Foldvari *et al.* (WO 99/11247, hereinafter "Foldvari") (Office Action, hereinafter "OA," at page 3). Applicants respectfully traverse this rejection.

Specifically, the rejected claims all recite a construct for transdermal delivery of an immunogen comprising at least one cationic sterol. The Examiner argues that Foldvari discloses sterols such as cholesterol, coprostanol, cholestanol, and cholestane. Furthermore, the Examiner states that "absent evidence to the contrary, the sterol of Foldvari is necessarily a cationic sterol." (OA at page 4). Applicants respectfully disagree. The term "cationic sterol" is defined in Dalsgaard on page 27, lines 8-9 as "a sterol carrying a net **positive** charge at pH 7.0" (emphasis added). Cholesterol, coprostanol, cholestanol, and cholestane are steroid precursors or metabolites, all of which carry a net **neutral** charge at pH 7.0. To illustrate this point, Applicants submit a

copy of pages from the Merck index (Exhibit A) describing compounds (5 $\alpha$ )-Cholestane (2199), Cholestanol (2200), Cholesterol (2201), and Coprosterol (also known as choprostanol) (2524). Applicants respectfully draw the Examiner's attention to the fact that none of these compounds have groups that are ionizable at pH 7.0. The claim is anticipated by a reference only if the reference teaches each and every element of the claim. (MPEP § 2131). Foldvari does not disclose a construct for transdermal delivery comprising *cationic* sterols, and thus does not anticipate any of the claims 1, 2, 4, 5, 9, 10, 13, 16, 18, 20, 21, 23, 25-27, 32, 34, 38-43, 46, 47, 49-55, 57, 60, and 61 .

Furthermore, in an effort to advance prosecution, and not in acquiescence to any pending rejections, Applicants have amended claim 1 to recite that the immunogen delivery system forms a complex which adopts a micro-particle structure in the form of a cage-like matrix. Support for this amendment is found at paragraph [0133] of the specification as filed, under the section entitled "Immunogen Delivery System." In addition, Dalsgaard, a U.S. patent application publication which has been incorporated by reference in its entirety into the present specification, specifies that the complexes of the present invention may adopt a microparticulate structure in the form of a "*cage-like* matrix similar to that known as an immune stimulating complex (Iscom)." (*See* p. 4, ll. 1-3 of Dalsgaard, emphasis added). The term "Iscom structure" is further defined in Dalsgaard as "*[r]igid cage-like* matrix characterized by an icosahedral symmetry" on page 2, ll. 21-24 (emphasis added).

In contrast, Foldvari discloses a composition of flexible lipid vesicles (liposomes) for transdermal administration of immunogen, wherein a lipid vesicle is composed of a series of *lipid bilayers*. Foldvari at p. 6, ll. 1-7 and Figure 1, emphasis added. Solely to

assist the Examiner, Applicants provide a figure from Chapter 9 entitled "Liposomes and ISCOMs" of "Novel Vaccine Strategies," S.H.E. Kaufmann (*ed.*) Wiley (2004), p. 174., attached as Exhibit B, comparing a diagrammatic representations and electron micrographs of liposomes (panel A) and ISCOMs (panel D). As can be seen from panel A, liposomes do not adopt the distinctive micro-particle structure in the form of a cage-like matrix typical of ISCOMs (panel D), and as required by the currently pending claims.

Lastly, the Examiner recites points 2-6 of the Applicants' previous argument and states that none of them were found persuasive. (OA at page 3-4). Applicants believe that these allegations are rendered moot by the above arguments. As such, it is respectfully requested that the Examiner withdraw the rejection.

***Rejections under 35 U.S.C. § 103(a)***

The Examiner has rejected claims 1, 2, 4-6, 9, 10, 13, 16-18, 20, 21, 23-27, 32-34, 38-43, and 46-61 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Foldvari and British Pharmacopoeia 1993 (herein after "BP"). (OA at page 8). Applicants respectfully traverse this rejection.

The factors to be considered under 35 U.S.C. § 103(a), are the scope and content of the prior art; the differences between the prior art and the claims at issue; and the level of ordinary skill in the pertinent art. *See Graham v. John Deere*, 86 S.Ct. 684 (1966) and MPEP §2141. This analysis has been the standard for 40 years, and remains the law today. *See KSR International Co v. Teleflex Inc.*, 127 S.Ct. 1727 (2007). The Office has recently published Examination Guidelines to aid Examiners in formulating obviousness rejections. *See Examination Guidelines for Determining Obviousness under 35 U.S.C.*

*103 in view of the Supreme Court decision in KSR International v. Teleflex Inc.* Fed. Reg. Vol. 72, pp. 57526 to 57535 (October 10, 2007), hereinafter "the Examination Guidelines." Seven rationales are suggested by which obviousness may be found, *e.g.*, by combining elements in the art or substituting one known element for another. As a common thread through all the rationales, the Examiner must establish on the record that a person of ordinary skill in the art would have recognized that the results of the combination or substitution were *predictable*. *Id.*, *e.g.*, at 57529.

The Examiner has not met the burden of establishing a *prima facie* case of obviousness based on the Examination Guidelines. Specifically, the Examiner has not established that the ordinary artisan reading Foldvari and BP in combination would arrive at the presently claimed construct for transdermal delivery of a complex comprising a saponin and a *cationic sterol* which adopts a *micro-particle structure* in the form of a *cage-like matrix*. Foldvari is directed to *flexible* lipid bilayer structures which *fully enclose* an oil in water emulsion. Nothing in Foldvari would even vaguely lead the skilled person to consider the use of rigid microparticles in the form of a cage-like matrix. Indeed, even the unskilled person would understand that an oil in water emulsion could simply not be contained by a microparticle with a cage-like matrix. Furthermore, the Examiner stated that Foldvari discloses sterols such as cholesterol, coprostanol, cholestanol, and cholestane, and that "absent evidence to the contrary, the sterol of Foldvari is necessarily a cationic sterol." (OA at p. 10). As discussed above, sterols disclosed in Foldvari are not cationic sterols, because none of them carry a net positive charge at pH 7.0.

With regards to the BP reference, the Examiner stated that it teaches wound dressings and medicated bandages, which include a semipermeable hydrocolloid dressing. (OA at p. 15). Furthermore, the Examiner argued that "it would have been obvious at the time the invention was made to use hydrocolloid dressing of British Pharmacopoeia 1993 because it is a sterile, self-adhesive, waterproof, multi-component structure that would be effective in delivering at least one immunogen to an individual." *Id.* Nothing in the BP reference cures the shortcomings of Foldvari as discussed above, nor would the BP reference predictably lead a skilled person to the elements missing from Foldvari such as the requirement for an immunogen delivery system comprising complex, which assumes a microparticle structure in the form of a cage-like matrix, and which comprises a cationic sterol. Therefore, the art cited by the Examiner would not have provided a reasonable expectation of success in obtaining the presently claimed cage-like complexes comprising cationic sterols because the mere substitution or combination of elements from the two references cited by the Examiner would not have predictably resulted in a construct for transdermal delivery of immunogenic agents comprising a complex formed of a saponin and a cationic sterol, which adopts a microparticle structure in the form of a cage-like matrix.

With respect to points 2-5 of the Applicants' previous arguments recited by the Examiner on pp. 9-16 of the OA, Applicants believe that the foregoing argument render the Examiner's contentions moot. Therefore, Applicant respectfully requests withdrawal of the rejection as it relates to the currently pending claims.

The Examiner further rejected claims 1, 2, 4, 5, 7-9, 10, 13, 16-27, 32-34, 38-43, and 46, 47, 49-55, and 57-61 under 35 U.S.C. § 103(a) as allegedly being unpatentable

over Foldvari and Lee *et al.*, *Intl. J. Pharm.* (2001) 221:1-22 (hereinafter as "Lee").

Applicants respectfully traverse this rejection.

Applicants respectfully contend that Examiner has not established that the ordinary artisan reading Foldvari and Lee in combination would arrive at the presently claimed construct. The Examiner stated that Foldvari discloses sterols such as cholesterol, coprostanol, cholestanol, and cholestane, and that "absent evidence to the contrary, the sterol of Foldvari is necessarily a cationic sterol." (OA at p. 17). As discussed above, sterols disclosed in Foldvari are not cationic sterols, because none of them carry a net positive charge at pH 7.0. The Lee reference discloses that hydrogels have been widely used as a drug carries. According to the Examiner:

It would have been obvious at the time the invention was made to use hydrogel because of its ease in manufacturing and self application (see Lee *et al.* at Page 10). Moreover, it would have been obvious at the time the invention was made to use the cross-linked hydrogel because all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention.

(OA at p. 21).

Just as with the BP reference, nothing in the Lee reference cures the shortcomings of Foldvari as discussed above, nor would the Lee reference predictably lead a skilled person to the elements missing from Foldvari such as the requirement for an immunogen delivery system comprising complex, which assumes a microparticle structure in the form of a cage-like matrix, and which comprises a cationic sterol. Therefore, for the reasons discussed above, the combinations of references cited by the Examiner would not have predictably led the skilled artisan to the presently claimed

cage-like complexes comprising cationic sterols just by performing the mere substitution or combination of elements from the two references.

With respect to points 2 and 3 of the Applicants' previous arguments recited by the Examiner on pp. 17-21 of the OA, Applicants believe that the foregoing argument render the Examiner's contentions moot. Therefore, Applicants respectfully request withdrawal of the rejection as it relates to the currently pending claims.

***Rejections under 35 U.S.C. § 112, first paragraph***

The Examiner rejected claims 23, 56, 58, and 59 under 35 U.S.C. § 112, first paragraph, as "containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor(s), at the time application was filed, had possession of the claimed invention." (OA at p. 22). Specifically, the Examiner stated that the phrase "an immunologically cross-reactive antigen" added to claim 23 did not appear in the specification or original claim as filed. Applicants respectfully disagree, but in an effort to advance prosecution, and not in acquiescence to the Examiner's rejection, Applicants have amended claim 23 to delete this phrase. Additionally, the Examiner stated that the phrase "microparticles with an average diameter of not more than 50 nm" added to claim 56 did not appear in the specification or original claim as filed. Again Applicants disagree, but in an effort to advance prosecution, and not in acquiescence to the Examiner's rejection, Applicants have amended claim 56 to substitute this phrase with "about 5 nm to 50 nm." Support for this amendment can be found in paragraph [0013] of the original specification, as filed. Lastly, the Examiner argued that phrases "rigid microparticles" and "case-like structures" added to claims 58 and 59, respectively, constituted new matter. Cancellation



of claims 58 and 59 render this rejection moot. Furthermore, Applicants respectfully point out that the amendment to claim 1, in which the immunogen delivery system complex “adopts a micro-particle structure in the form of a cage-like matrix” is clearly described in the present application at paragraph [0133] in a section headed “Immunogen Delivery System” notes that the complexes: “in one preferred embodiment ***adopt a micro-particle structure in the form of a cage-like matrix*** similar to that known as an immune stimulating complex (iscom)” (emphasis added). Therefore, Applicants respectfully request withdrawal of the rejection as it relates to the currently pending claims.

***Rejections under 35 U.S.C. § 112, second paragraph***

The Examiner rejected claims 1, 2, 4-10, 13, 16-18, 20, 21, 23, 25-27, 32, 34, and 38-61 under 35 U.S.C. § 112, second paragraph, as “being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.” (OA at p. 23). The Examiner, however, has not pointed to any specific phrases or terms which allegedly render the claims vague or indefinite. The Examiner did make some specific 35 U.S.C. § 112, second paragraph rejections of earlier-pending claims in the previous non-final Office Action mailed on October 3, 2008. In the pending Office Action at p. 2, however, the Examiner indicated that these rejections had been withdrawn. Insofar as the Examiner meant to reject claims 1, 2, 4-10, 13, 16-18, 20, 21, 23, 25-27, 32, 34, and 38-61 under 35 U.S.C. § 112, second paragraph, Applicants respectfully traverse. Should the Examiner maintain the rejection, Applicants respectfully ask the Examiner to point out any specific concerns.

Additionally, the Examiner rejected claim 59 as being vague and indefinite by the use of the term "case-like structure". Applicants respectfully submit that cancellation of claim 59 renders this rejection moot.

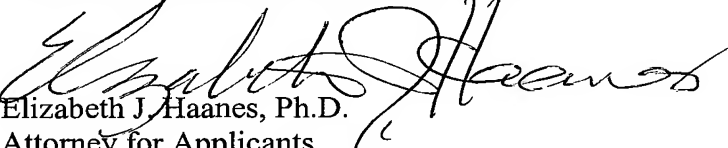
### ***Conclusion***

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicant therefore respectfully requests that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicant believes that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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